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Effect of dexmedetomidine or propofol sedation on haemodynamic stability of patients after thoracic surgery

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Abstract

Background: Dexmedetomidine and propofol are commonly used sedative agents in non-invasive ventilation as they allow for straightforward arousal and are easily controllable to a relative degree. Moreover, dexmedetomidine is associated with a low risk of respiratory depression. However, both agents are associated with significant haemodynamic side effects. The primary aim of this study is to compare the influence of both drugs on haemodynamic effects in patients after thoracic surgical procedures receiving dexmedetomidine or propofol for non-invasive postoperative ventilation.

Methods: A prospective, randomised, observational study conducted in a university hospital. Interventions: Continuous sedation with dexmedetomidine or propofol for six hours of postoperative non-invasive ventilation after thoracic surgery, with concomitant use of continuous epidural analgesia.

Results: A total of 38 patients (20 on dexmedetomidine and 18 on propofol) were included in the analysis. The primary findings of this study were that although the heart rate, along with the systolic and mean arterial blood pressure did not differ significantly between the groups ($P = 0.87$; $P = 0.42$; $P = 0.13$, respectively), diastolic arterial blood pressure was significantly higher in the propofol group ($P = 0.02$). A comparative analysis of epinephrine usage did not reveal significant differences between the groups. Although cardiac output ($P = 0.36$) and cardiac index ($P = 0.36$) analyses did not show significant differences between the groups, there is a clear tendency toward lower values of CO/CI in the group receiving propofol. While we also observed a similar tendency in the stroke volume index and stroke volume variation values, these differences did not reach statistical significance either ($P = 0.16$; $P = 0.64$, respectively). Despite systemic vascular resistance index values being higher in the propofol group, exceeding reference values, similarly, the difference between the groups was not significant ($P = 0.36$).

Conclusions: The main finding of this study is that dexmedetomidine and propofol provide similar advantages in haemodynamic stability during short-term sedation for non-invasive ventilation after thoracic surgical procedures in patients receiving continuous epidural analgesia.

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Key words: thoracic surgery, postoperative period; sedation; sedatives, dexmedetomidine; sedatives, propofol; haemodynamics, monitoring

Patients undergoing lung resection surgical procedures are considered one of the groups at the highest risk of developing intraoperative and postoperative complications [1]. This is associated with preoperative patient-related factors, such as frequently present significant comorbidities affecting the respiratory system (asthma, chronic obstructive pulmonary disease, COPD) and the cardiovascular system (arterial hypertension, chronic heart failure, atrial fibrillation etc), as well as surgical and anaesthetic techniques necessary for performing an efficient and safe surgical procedure

(thoracic epidural anaesthesia, one lung ventilation [OLV]). One of the postoperative complications encountered in patients who underwent OLV after thoracic surgery procedures is lung atelectasis, which can increase the prevalence of other pulmonary postoperative complications such as pneumonia and respiratory failure [1, 2]. One of the methods useful in preventing postoperative atelectasis is non-invasive ventilation (NIV) with continuous positive airway pressure (CPAP). This allows for proper lung aeration and reduces the degree of atelectasis [3]. Unfortunately, in the vast majority of patients it is poorly tolerated and usually requires mild to moderate sedation. Sedation, often paired with analgesia, is also one of the principal features of Goal-Directed Mechanical Ventilation (GDV), used to maintain the spontaneous activity of a respiratory centre and provide the necessary comfort and acceptance of ventilation. The goal of sedation in mechanically ventilated patients is to keep them calm and without agitation in order to maximise patient comfort and ventilator synchrony [4–6].

There are numerous agents used for the sedation of patients during NIV in the postoperative period. They are divided into several different classes, each with distinct pharmacokinetic and pharmacodynamic properties, and different side-effect profiles that may limit their use or make them more suitable for certain groups of patients. While choosing an optimal sedation agent for their patient, clinicians must not only take into account the efficacy but also side effects, such as haemodynamic instability or the prevalence of delirium. One of the sedative drugs that is still gaining popularity and becoming more widely used is dexmedetomidine, a highly selective α2-adrenoceptor agonist. It has sedative, analgesic and opioid-sparing effects and is suitable for short-term sedation in an intensive care setting [7]. Dexmedetomidine has been studied in two randomised, double-blind, multicentre MIDEX (compared with midazolam) and PRODEX (compared with propofol) trials, the results of which concluded that longer-term sedation with dexmedetomidine was non-inferior to midazolam and propofol in terms of time spent at the target sedation range, as well as being associated with a shorter time to extubation than midazolam or propofol, and a shorter duration of mechanical ventilation than midazolam. Patients receiving dexmedetomidine were also easier to rouse, more co-operative and better able to communicate than patients receiving midazolam or propofol [8]. Dexmedetomidine also had beneficial effects on reducing the prevalence of delirium in some randomised controlled trials [9]. It has gained attention in the adult, paediatric and geriatric populations, predominantly because of its feature of causing minimal respiratory depression. Additionally, beyond its well-known advantages, dexmedetomidine has recently been investigated for its potential in other clinical scenarios, including neuroprotection, cardioprotection and renoprotection, and the results of studies are promising [10].

The goal of this study is to compare dexmedetomidine with propofol in short-term sedation for NIV in patients after thoracic surgery procedures.

METHODS

This prospective, randomised, observational study was conducted in a university hospital following approval by the Ethics Committee of the Medical University of Silesia. The study protocol was designed in accordance with Consort 2010 guidelines (http://www.consort-statement.org).

Patients who gave informed written consent and were scheduled for elective lung tissue resection by anterolateral open thoracotomy were enrolled in the study. Other inclusion criteria were: an age of 18–70 years; American Society of Anesthesiologists (ASA) status I–III; body mass index (BMI) 19–30 kg m^{-2}; and no contraindications for drugs and anaesthesia techniques used in the protocol. The exclusion criteria were as follows: a lack of consent; significant coagulopathy; contraindications to epidural anaesthesia or drugs used in the protocol; chronic pain and chronic pain medications intake; chest wall neoplastic invasion; visible thoracic spine deformities; previous spinal surgery; and obesity (BMI > 30 kg m^{-2}).

During a preliminary assessment of the patients, we recorded age, sex, height, weight and BMI, blood pressure (systolic, diastolic, mean), and the presence of any significant comorbidities. After recording above-mentioned parameters, each patient was randomly assigned into one of two groups: in the first group, dexmedetomidine (Dexdor, Orion Corporation, Finnorszag, Finland) was used as a sedative agent for NIV; while in the second group, propofol (*Plofed 2%*, *Polfa Warszawa*, *Warsaw*, *Poland*) was used as a sedative agent for NIV. Randomisation numbers were generated by a computerised random number generator.

Anaesthetic management was identical in both groups. Patients were premedicated one hour before arriving in the operating theatre with oral midazolam. After arriving in the operating room, the patient was transferred to an operating table, an 18 G intravenous cannula was inserted in the forearm and intravenous fluid therapy was initiated. Simultaneously, non-invasive haemodynamic monitoring was commenced with the use of a ClearSight finger cuff (*Edwards Lifesciences*, *Irvine*, *USA*) device used on distal phalanx of the 2^{nd}, 3^{rd} or 4^{th} finger. The cuff had been prepared and fitted earlier. We continuously measured cardiac output (CO; L min^{-1}), cardiac index (CI; L $min\ m^{-2}$), stroke volume index (SVI; mL m^{-2}), stroke volume variation (SVV; L $min\ m^{-2}$), systemic vascular resistance index (SVRI; dyn sec cm^{-5} m^{-2}) through the entire course of surgery and PACU stay.

Intraoperative and postoperative analgesia was based on thoracic epidural analgesia. Before the induction of anaesthesia, the anaesthetist attending the case installed a epidural catheter in the thoracic epidural space (at levels T3 to T8) that was identified by the "hanging drop" technique with a Tuohy 18G needle. A 20 G epidural catheter was then advanced 3–4 cm beyond the tip of the Tuohy needle and, after being connected with an antibacterial filter, fastened to the skin with a dedicated sterile dressing. After fixing the catheter, a test dose of 3 ml of bupivacaine solution with epinephrine (5 mg + 0.005 mg mL^{-1}) was given to confirm the right localisation of the catheter in the epidural space.

General anaesthesia was induced with a combination of propofol at approximately 2 mg kg^{-1}, cisatracurium at approximately 0.15 mg kg^{-1}, and fentanyl at approximately 2 µg kg^{-1}. Additional doses were given as clinically indicated. Patients were intubated using a left-sided double lumen tube of adequate size and, after confirming correct placement of the tube, mechanical ventilation was started. Patients were then placed in a non-operated side position. Anaesthesia was maintained using sevoflurane in 100% oxygen (FiO_2 = 1.0) while fractioned doses of fentanyl and cisatracurium were administered as needed. During general anaesthesia, patients received fluids (Ringer's lactate solution) at 4 mL kg^{-1} h^{-1}. In case of bradycardia (defined as a decrease in the heart rate exceeding 20% of baseline values), the patient was given 0.01–0.015 mg kg^{-1} of *i.v.* atropine. In cases of hypotension (defined as a decrease in mean arterial blood pressure below 70 mmHg or more than 25% of baseline value patients were given ephedrine in fractionated 5 mg *i.v.* doses (maximum dose 25 mg), and, if this was not effective, a continuous infusion of norepinephrine was commenced using a syringe pump, titrated to achieve a mean arterial pressure above 70 mm Hg.

Immediately after the end of the surgery, a continuous epidural infusion of 0.0625–0.1% bupivacaine with a 0.0006% fentanyl solution was commenced with the infusion rate calculated based on a modified Bromage formula (0.8 mL per segment plus 0.05 mL for every 5 cm over 150 cm of the patient's height). According to multimodal analgesia regimens, 1g *i.v.* paracetamol was given to all patients at 6 h intervals. Ketoprofen was given as a rescue medication if necessary once in 12 h, not to exceed the maximum daily dose. We aimed to achieve pain intensity below 3 on the VAS scale in all patients.

After the surgical procedure patients were transferred into post-anaesthesia care unit (PACU) and were carefully monitored. While they were being aroused from anaesthesia, a continuous infusion of sedatives was started. In the first group (PRO), patients were given propofol at 1 to 4 mg kg^{-1} h^{-1}, while in the second group (DEX), patients were administered dexmedetomidine at 0.7 to 2.0 ug kg^{-1} h^{-1}. The infusion rate and dose was adjusted to achieve a sedation level between –1 and –3 on the Richmond Agitation-Sedation Scale (RASS) which corresponds to voice arousal. When the patient fulfilled extubation criteria, the endotracheal tube was removed and NIV-CPAP ventilation was started using a dedicated face mask (NovaStar TS NIV Full-Face Mask; Dräger, Lübeck, Germany). Ventilation parameters were adjusted to achieve 4–8 mL kg^{-1} h^{-1} with adequate oxygenation at FiO_2 0.2–0.3. This regimen was maintained for the next 6 hours while the patients were continuously monitored. We measured electrocardiography (ECG), heart rate (HR; beats min), blood saturation (SpO_2: percentages), non-invasive blood pressure (NIBP; mm Hg), sedation level on the Richmond Agitation and Sedation Scale (RASS), pain intensity level on the Visual Analogue Scale (VAS) and the Prince Henry Hospital Pain Score (PHHPS). Similarly to Ławicka *et al.* [11], in measuring haemodynamic parameters using the non-invasive method, the ClearSight device was used to measure CO, CI, SVI, SVV, SVI and SVRI [11]. Data were recorded every hour. Additionally, patients were evaluated for adverse events, such as hypotension, bradycardia, delirium or agitation.

STATISTICAL ANALYSIS

Data were analysed using Statistica 12.0 (StatSoft, Tulsa, USA) and were assessed for normality using the Shapiro-Wilk test. Normally distributed data were analysed using Student's t test for independent variables. The variability of the parameters in time and between the groups was analysed with a parametric analysis of variance for multiple measurements (ANOVA) and post-hoc Bonferroni correction where applicable. A P-value < 0.05 was considered statistically significant.

RESULTS

During the study period, 50 patients were screened for this study. A total of 44 patients fulfilled the inclusion and exclusion criteria and were randomly assigned to two study groups, resulting in 22 patients in each group. Overall, six patients were excluded after randomisation: 2 in the DEX group and 4 in the PRO group (Fig. 1) due to violations in the study protocol or adverse events. The thoracic surgical procedures performed in the study population are listed in Table 1.

Finally, thirty eight patients (20 males and 18 females) completed the study. Propofol-based sedation was administered in 18 patients, while dexmedetomidine was given to 20 patients. There were no significant differences between the groups in age (P = 0.76), BMI (P = 0.52), SBP and DBP measured before the surgery (P = 0.42; P = 0.49, respectively) and ASA physical status (P = 0.51).

Although systolic and mean arterial blood pressure did not differ significantly between the groups (P = 0.42; P =

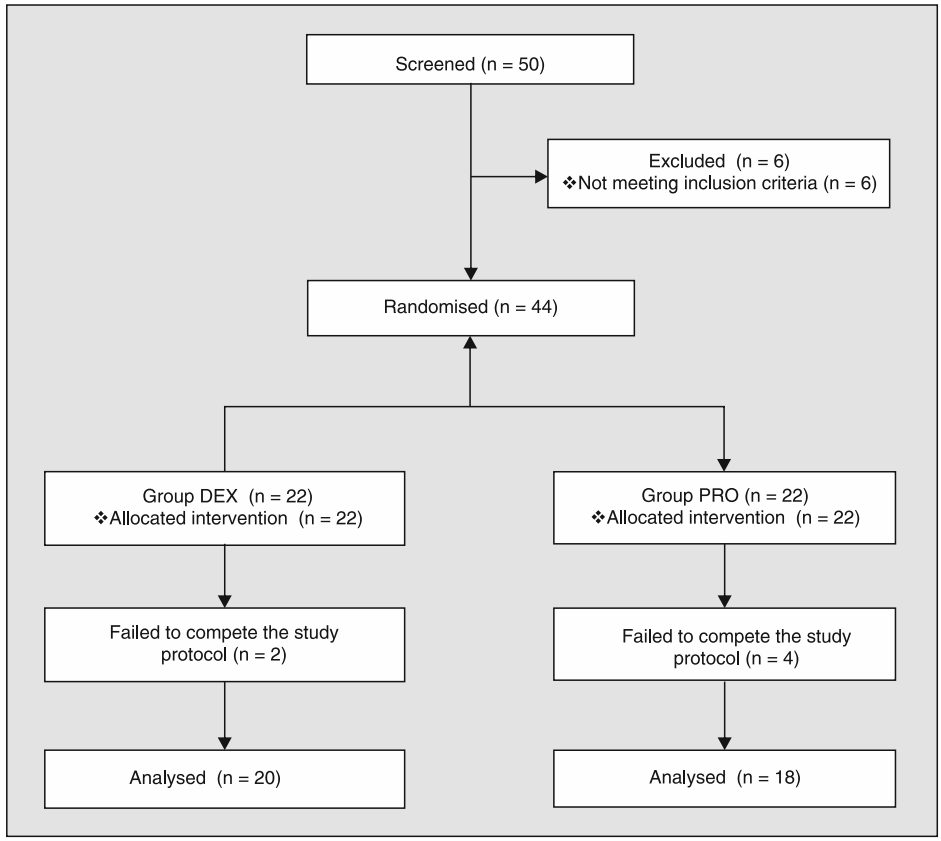

Figure 1. A CONSORT diagram of patient flow in the randomised trial

Table 1. Surgery types in study groups

Type of surgery	PRO group n = 18	DEX group n = 20
Lung resection	1	0
Double lobectomy	4	3
Pulmonary lobectomy	8	10
Lung parenchymal resection	4	6
Other	1	1

0.13, respectively), diastolic arterial blood pressure was significantly higher in the PRO group ($P = 0.02$) (Fig. 2). HR variations also did not differ significantly between the groups ($P = 0.87$) (Fig. 3). A comparative analysis of epinephrine usage did not reveal significant differences between the groups ($P = 0.43$).

Although CO and CI analyses did not show significant differences between the groups ($P = 0.36$; $P = 0.36$, respectively), there is a clear tendency toward lower values of CO/CI in the group receiving propofol for sedation (Fig. 4). While we also observed similar tendency in SVI and SVV values, these differences did not reach statistical significance either ($P = 0.16$; $P = 0.64$, respectively). There is also a visible difference between the values in time — SVI and SVV were significantly higher starting from the second hour compared with the first measurements.

Although SVRI values were higher in the PRO group, exceeding reference values, similarly, the difference between the groups was not significant ($P = 0.36$). There was a marked decrease in SVRI in both groups starting from hour 3 of the study (Fig. 5).

DISCUSSION

The main finding of this study is that dexmedetomidine and propofol provide similar advantages in haemodynamic stability during short-term sedation for non-invasive ventilation after thoracic surgical procedures in patients receiving continuous epidural analgesia. Although we observed more pronounced variations in haemodynamic parameters in the group treated with propofol, the difference between the groups did not reach statistical significance, except for diastolic arterial pressure which was higher in the PRO group. We also did not observe significant bradycardia and hypotension, as well as serious adverse events during the course of the study.

Both drugs used for sedation in our study have well-known features that can lead to cardiovascular depression. One of the known effects of large concentrations of dex-

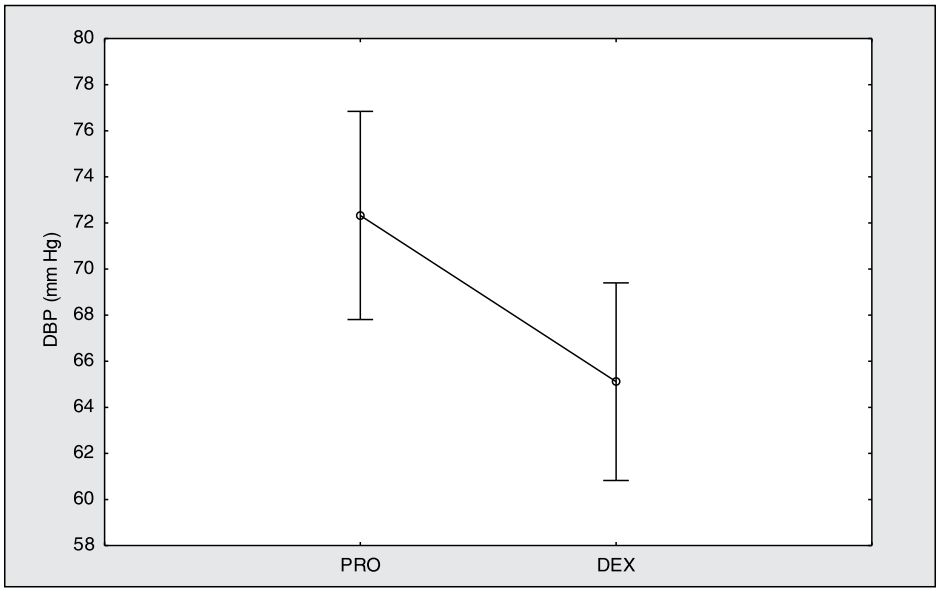

Figure 2. Mean and 95% CIs of diastolic blood pressure (DBP mm Hg) in study groups. Statistically significant higher ($P = 0.02$) values DBP were observed in the PRO group

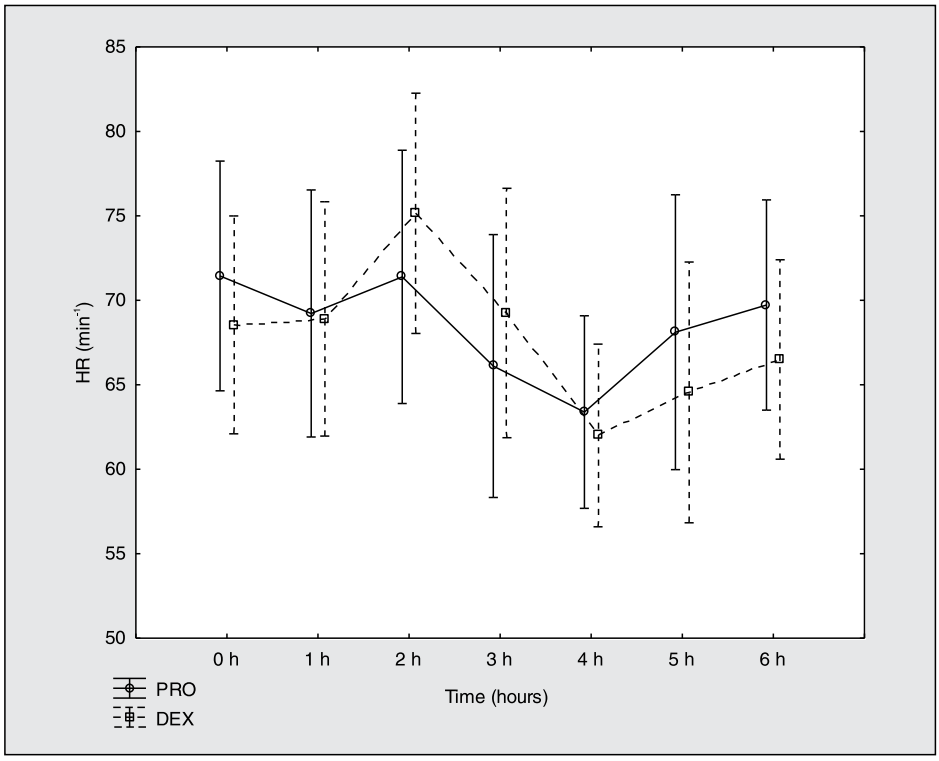

Figure 3. Mean and 95% CIs of heart rate per minute (HR) during consecutive time points. "0h", "1h", "2h", "3h", "4h", "5h", "6h" refer to the time in hours from the beginning of sedation. No significant statistical differences were found between the studied groups at any point in time

medetomidine or of rapid administration of dexmedetomidine (for example as a loading dose) is the activation of α_2-receptors on vascular smooth muscle, which can result in transient vasoconstriction that produces increases in MAP, and possibly a reflex decrease in HR. After the initial effect of dexmedetomidine on peripheral α_2-receptors, a more gradual central effect predominates, including sedation and a decrease in sympathetic outflow and circulating catecholamine levels [12, 13]. This latter effect may be expected to cause decreases of HR and MAP. Dexmedetomidine also

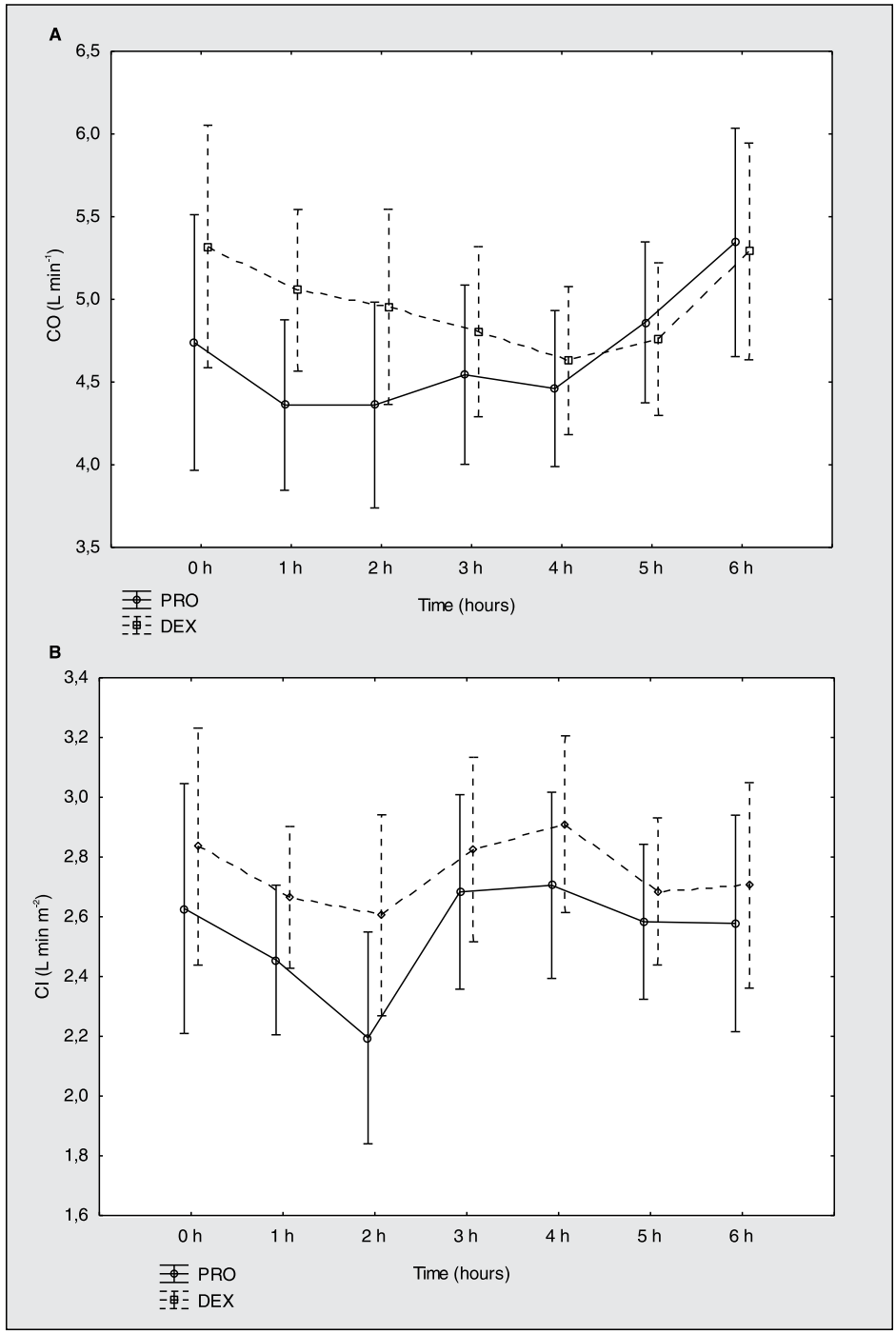

Figure 4. Mean and 95% CIs of (A) cardiac output (CO; L min^{-1}), (B) cardiac index (CI; L min m^{-2}), during consecutive time points. "0h", "1h", "2h", "3h", "4h", "5h", "6h" refer to the time in hours from the beginning of sedation. No significant statistical differences were found between the studied groups at any point in time

may decrease HR via a vagal mimetic effect [13]. In our study we did not observe severe bradycardia in subjects treated with dexmedetomidine in comparison with subjects treated with propofol, even though both groups were also receiving continuous epidural analgesia. Perhaps this may be associated with not administering the loading dose in the dexmedetomidine group. Propofol on the other hand was shown to have a powerful inhibitory effect on sympathetic outflow. In our study, there were no differences in postoperative MAP between treatment groups despite the well-known sympathoinhibitory effects of dexmedetomidine. This may have been the result of a similar decreasing of MAP in the propofol-treated group. Other authors have found different results — a significant difference in MAP

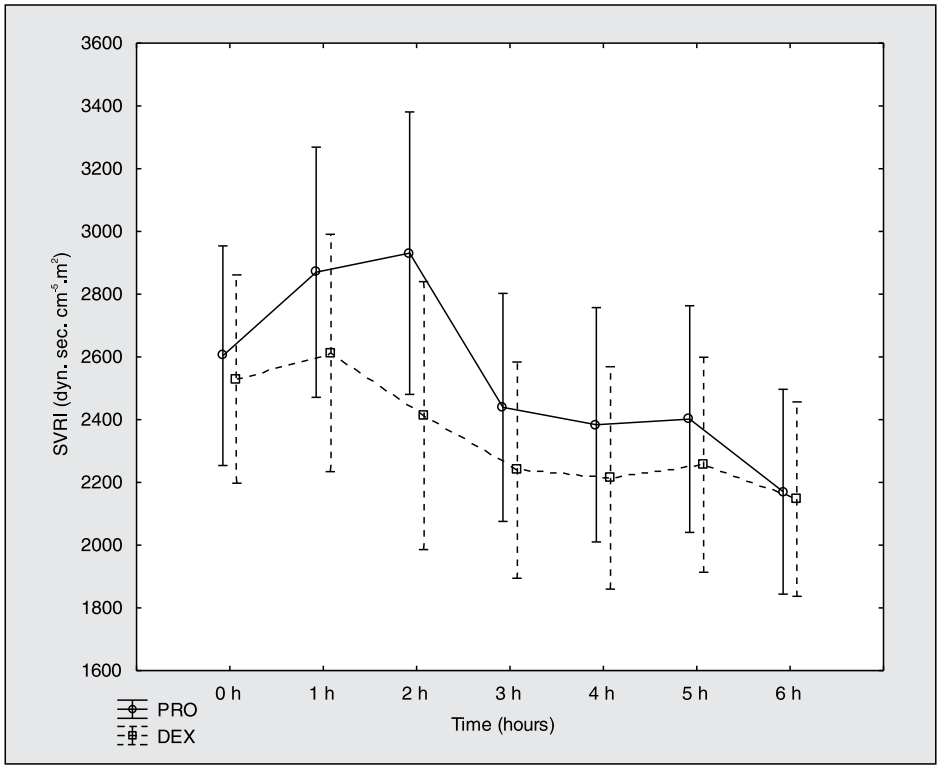

Figure 5. Mean and 95% CIs of systemic vascular resistance index (SVRI; dyn. sec. cm^{-5} m^{-2}), during consecutive time points. "0h", "1h", "2h", "3h", "4h", "5h", "6h" refer to the time in hours from the beginning of sedation. No significant statistical differences were found between the studied groups at any point in time

which was higher with dexmedetomidine compared with propofol [14]. The difference between these studies and our study is the sample size. This is quite small in our trial and constitutes its main limitation. Moreover, both groups were treated by TEA which also influences haemodynamic stability via the sympathetic blockade. West *et al.* also compared the haemodynamic effects of dexmedetomidine and propofol as sedative agents on a larger group of participants (n = 300) and found results more similar to those presented in this study. However, the data are not fully comparable because of different indications for sedation, times of sedation (min. four hours) and lack of epidural analgesia. The authors also found differences between the groups sedated with propofol and dexmedetomidine (more bradycardia in the dexmedetomidine group and more hypotension in the propofol group) but without statistical significance [15]. Erdman *et al.* [16] studied the prevalence of serious haemodynamic adverse events (severe hypotension defined as mean arterial pressure < 60 mm Hg) and bradycardia defined as a heart rate < 50 beats/min) in neurocritical care patients sedated with either dexmedetomidine or propofol and concluded that it was similar between the groups. These results are similar to our study although our prevalence of haemodynamic serious adverse events was lower. On the other hand, Tufair *et al.* [17] compared the effects of anaesthesia by dexmedetomidine and propofol on haemodynamic variables in patients scheduled for elective cardiac surgery and found HR and MAP were significantly lower in the dexmedetomidine group compared with the propofol group ($P < 0.05$). Both of the groups had a similar requirement of vasopressors and inotropes. Finally, the main limitation of our study is its small sample size.

CONCLUSION

In conclusion, in our study both propofol and dexmedetomidine appeared to be safe and acceptable sedative agents for non-invasive ventilation after thoracic surgical procedures in patients receiving continuous epidural analgesia.

The cardiovascular response of patients receiving continuous epidural anaesthesia and sedated for non-invasive ventilation with dexmedetomidine is similar to that of patients sedated with equipotent doses of propofol. These properties, combined with the analgesic qualities and lack of respiratory depression seen with dexmedetomidine, can have advantages for patients from certain risk groups such as significant chronic obstructive pulmonary disease. However, further research, especially on a larger group of subjects, is necessary.

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